Medical and Pediatric Oncology Supplement 1:1–9 (1998)

Radiation Injury to the Central Nervous System

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INTRODUCTION

In the treatment of primary or metastatic malignancies of the central nervous system (CNS) by ionising radiation, consideration has been given to the risk of developing adverse reactions, even death, as a consequence of the treatment. Changes may occur from a few months to many years after the completion of therapy. In the treatment of children and adolescents with cancer, there is an increased concern because of the potential long survival times and the risks of impairing intellectual development. In the treatment of young children, in particular, an assumption is made frequently of an increased vulnerability due to the immaturity of the brain. However, no age-dependent, maximum tolerable doses have been determined with any certainty, even though it is known that the postnatal development of the brain, which is characterised by the formation of dendrites and synapses, the proliferation of glial cells, and the myelination of central pathways, is not complete until nearly the end of the second decade of life [1].

DELAYED INJURY TO THE CNS AND ITS PATHOGENESIS

The most commonly reported lesion in the CNS after therapeutic irradiation is selective coagulation necrosis of white matter [2]. At doses close to the threshold for this effect, scattered focal areas of necrosis may be seen, which mineralise with time or become associated with the appearance of compact astroglial scars. Slightly higher doses may produce large necrotic areas, resulting in severe neurological impairment and, in some cases, death. This lesion is frequently referred to as early delayed damage, and it is seen most commonly within the first year following the completion of radiotherapy.

A somewhat later occurring lesion (late delayed damage) is characterised by the development of chronic types of vascular change, e.g., telangiectasia, hyaline, and fibrinoid changes in the wall of vessels. These lesions may be asymptomatic and have no direct relationship to necrosis or any neurological deficiency. The occurrence of an acute vascular accident as a result of one of these abnormalities is cause for concern and may result in death [3].

More recently, a generalised and progressive atrophy of nervous tissue has been reported without clear signs of necrosis or vascular injury. This has been quantified on computerised tomography scanning [4] in dog brain and is associated with primary demyelination in human brain [5].

Early Delayed Injury

For many years, the underlying pathological mechanisms that are responsible for the development of selective white matter necrosis in the CNS were the subject of extensive debate. Numerous theories have been proposed that can be categorised best into two broad groups: 1) White matter necrosis is caused by the reproductive death of glial cells or their precursors, and this leads to the development of demyelination and necrosis; or 2) radiation acts primarily on the vasculature, and any necrosis is secondary to ischemia [6].

Evidence from recent experimental studies in the rat has provided support for a vasculature-mediated mechanism and against any direct involvement associated with the reproductive sterilisation of glial progenitors. Quantitative studies in the irradiated brains of mature rats [7] have shown a significant reduction in the number of endothelial cell nuclei and of blood vessels in white matter prior to the development of necrosis. There were no significant changes in oligodendrocyte number in non-necrotic tissue. These vascular effects were associated with various reactive changes that could be quantified. These included blood vessel dilatation, endothelial nuclear enlargement, blood vessel wall thickening, and astrocyte cytoplasmic hypertrophy. Significant astrocyte hyperplasia was also demonstrated. These various features were referred to collectively as a ‘‘tissue injury unit’’: they increase in both incidence and severity with time after irradiation. In the fimbria of the rat brain, the latency time for a 50% incidence of these individual or combined effects preceded the time of development of necrosis by at least 10 weeks (Fig. 1). When the severity of each of these phenomena was assessed on a score of 1–3 [8], a clearly defined relationship between the severity of the tissue injury unit score and demyelination/necrosis was found (Fig. 2).

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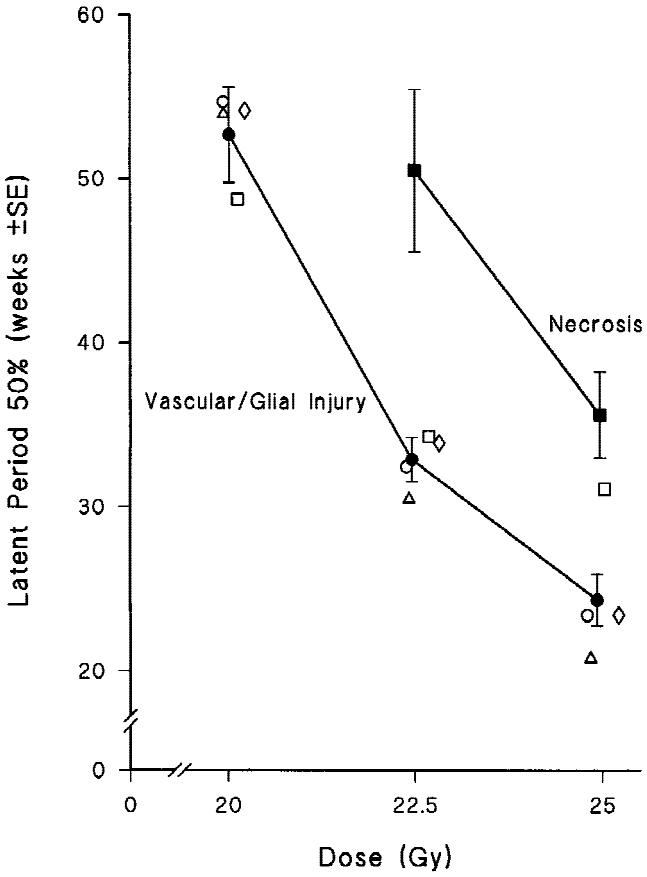

Fig. 1. Dose-related changes in the latency associated with a 50% incidence of white matter necrosis (solid squares) and different components of a tissue injury unit (TIU); blood vessel dilation (open circles), endothelial cell enlargement (triangles), blood vessel wall thickening (open squares), and astrocyte hypertrophy (diamonds), plus a combined TIU (solid circles). Studies in the fimbria of the rat brain. Reproduced from Calvo et al. [7].

There were many additional changes noted in these series of experiments that were not quantified. Of specific interest was the adhesion of lymphocytes to the endothelial wall of blood vessels. Diapedesis has been identified subsequently as a significant factor in semithin sections of irradiated rat brain (Reyners et al., personal communication). The accumulation and perivascular infiltration of lymphocytes was also reported in the microcirculation of the pig spinal cord after irradiation and prior to the onset of white matter necrosis [9,10]. There have been no direct investigations so far to demonstrate the up-regulation of adhesion molecules on the surface of endothelial cells after irradiation; however, by extrapolation from other disease processes [11] that involve the CNS, this is likely to be the case. Other changes in endothelial cell function, such as increased vascular permeability [12] and progressive development of an imbalance in the ratio of two key eicosanoids, thromboxane and prostacyclin [13], are also factors that need to be considered in the understanding of early delayed radiation-induced injury to the CNS.

Evidence against the direct involvement of glial progenitor cells in the development of this lesion has come from irradiation studies with thermal neutrons that using a rat spinal cord model [14]. Irradiation was with the thermal neutron beam alone or with the beam in combination with a boron-neutron capture agent. The local distribution of the capture agent can be used to modify the distribution of the radiation dose between the vascular endothelium and the CNS parenchyma. One neutron capture agent borocaptate sodium (BSH) does not cross the blood-brain barrier; hence, a high local dose from the neutron capture reaction ($^{10}B + n \rightarrow {}^{7}Li + {}^{4}He$) will be delivered to the vasculature when there are high levels of ^{10}B in the blood. Another capture agent, boronated phenyl alanine (BPA), crosses the blood-brain barrier; hence, the dose from the neutron capture reaction will be more equal to both the parenchymal and vascular elements. Despite the difference in dose distribution produced by thermal-neutron irradiation in the presence of the two different neutron capture agents, early delayed damage involving the selective necrosis of white matter was still induced. Dose-effect relationships for this end point have been established, and ED_{50} values for this effect have been calculated [15].

In another series of studies, the spinal cords of animals were irradiated with doses isoeffective for the late CNS effect, i.e., one-third of the ED_{50} value [14]. (ED_{50} is the dose required to produce matter necrosis in 50% of the animal's irradiation.) Irradiation was carried out with thermal neutrons alone or with thermal neutrons in combination with either BSH or BPA. The spinal cords were removed from animals 1 week after irradiation, and the irradiated segment was disaggregated and assayed for the survival of glial progenitors. Glial progenitor cell survival was very high (0.46 ± 0.15 s.d) in the group that received thermal neutron irradiation with BSH as the capture agent. This compared with the use of BPA as the neutron capture agent, with which progenitor survival was only 0.09 ± 0.05 (s.d). The corresponding value for thermal neutron alone, 0.03 ± 0.02 (s.d) was similar to that for the extrapolated one-third ED_{50} dose for 6 MV X-rays: a single dose of 12.5 Gy. These studies with isoeffective doses for late damage clearly show the relative importance of the vascular endothelium, as opposed to the reproductive sterilisation of glial progenitor cells, in the events leading to the expression of white matter necrosis.

Late Delayed Injury

The late change in the CNS has not been studied as extensively as the early delayed lesion. It has been documented in the rat brain and spinal cord [16,17]. The distribution of gross vascular abnormalities was estab-

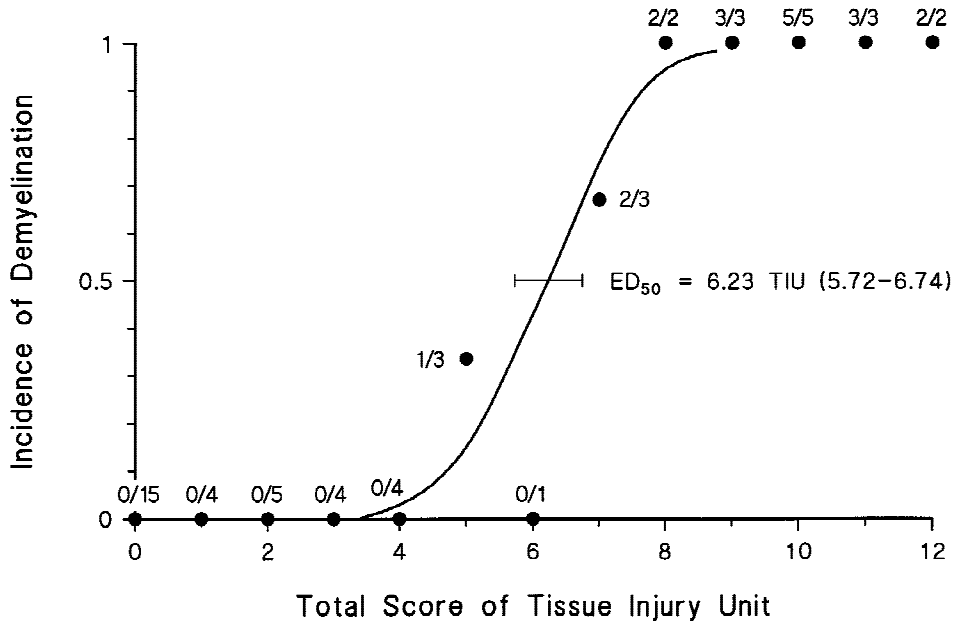

Fig. 2. Relationship between the incidence of white matter necrosis in the fimbria of the rat brain and the severity of the TIU score. Reproduced from Reinhold et al. [8].

lished by using a microangiographic method, as was the time-related incidence of such lesions [17]. The latent period for a 50% incidence of gross vascular abnormalities was 86.5 weeks after a single dose of 20 Gy. A similar time course has been noted for the development of telangiectasis in human skin after radiotherapy. It has been suggested that there may be a link between the appearance of the vascular abnormality and the atrophy of smooth muscle cells in arterioles [7].

Progressive CNS Atrophy

This phenomenon has not been well studied but may result from a loss of glial cells or their progenitors. This syndrome may be of clinical importance, because it has been observed after clinically relevant doses that are not associated with a significant risk of necrosis or late vascular injury [18]. Such changes, if they were to occur in children, could provide a basis for the impaired development of intellectual ability.

RATIONALE AND PROSPECTS FOR THE PROPHYLACTIC TREATMENT OF RADIATION LATE EFFECTS IN THE CNS

For early delayed irradiation injury, there is now sufficient evidence to implicate a progressive loss of endothelial cells and/or a reduction in vascular density as the initiator of a cascade of changes leading to overt white matter necrosis. Although some of the morphological representations of that cascade have been identified, the underlying molecular and biochemical changes are still the subject of much speculation. Possible explanations of how endothelial cell loss may lead to white matter necrosis, either by an increase in vascular permeability and/or an up-regulation to adhesion molecules, are illustrated in Figure 3. The appearance of swollen or hypertrophic astrocytes suggests a selective and subtle change in the integrity of the blood-brain barrier, resulting in the accumulation of more water in the CNS parenchyma. This increase in the water content of the brain, as a late consequence of irradiation, has been confirmed in the rat brain by direct measurements of water content [19]. Perivascular oedema [10] with raised intracranial pressure would produce ischaemia. Any reperfusion would act to amplify the effect.

Other CNS pathologies, e.g., acute experimental allergic encephalitis, which also shows evidence of lymphocyte adherence and perivascular cuffing, are reported to be associated with an increased expression of adhesion molecules on the endothelial cell surface [11]. Such pathologies have also demonstrated that lymphocyte infiltration is associated with cytokine expression (TNF/LT; tumour necrosis factors α and β, respectively). In vitro studies have shown that these cytokines can produce astrocytic hypertrophy and hyperplasia, which are features of the radiation response, and apoptosis of oligodendrocytes [20,21]. White cell adherence to the endothelium is also associated with CNS ischaemia and reperfusion injury. Clearly, with such a complexity of response, intervention, if it is targeted properly, could be effective in modulating the outcome that is usually associated with a given radiation dose.

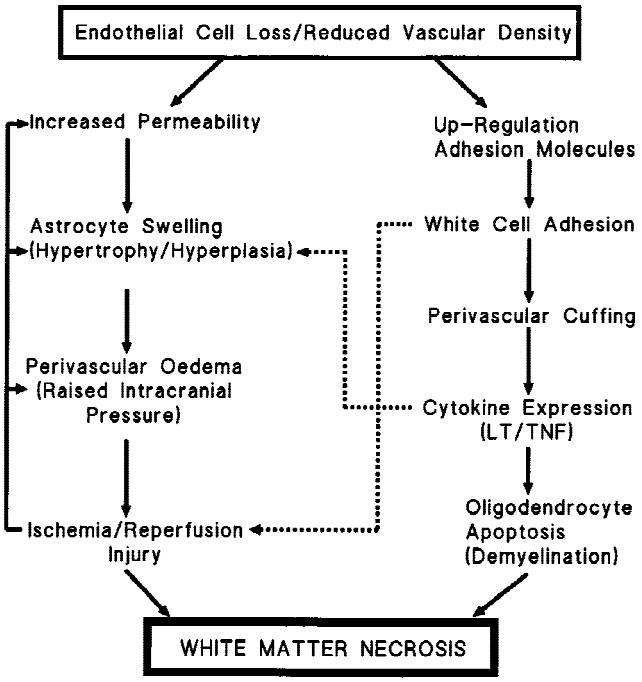

Fig. 3. Schema suggesting possible reactive cascades relating to endothelial cell loss to the eventual development of white matter necrosis in the central nervous system. TNF/LT, tumour necrosis factors α and β.

The premise that white matter necrosis was a consequence of reperfusion injury following the development of increased vascular permeability led Hornsey et al [22] to use the iron-chelating agent, desferrioxamine, in the prophylactic management of spinal cord injury. Iron is the catalyst that converts superoxide radicals or H_2O_2 into damaging hydroxyl radicals in reperfusion-related damage [23]. In this study, rats were fed a low-iron diet from 85 days after local irradiation of the spinal cord and were administered desferrioxamine from day 120 (30 mg in 0.3 ml subcutaneously, 3 × week). The time of the start of drug administration coincided with the initial detection of vascular permeability changes. The timing of the development of ataxia, due to white matter necrosis, was delayed and the incidence of lesions was reduced after single doses of 25 Gy and 27 Gy (Fig. 4). Dexamethasone was also shown to delay the development of or to reverse radiation-induced paresis and/or paraplegia along with producing a marked reduction in regional capillary permeability. Indomethacin, on the other hand, failed to influence any of these parameters [24].

In an alternative approach, 20-carbon polyunsaturated fatty acids (PUFAs) were used [25]. It was suggested that a modification in dietary PUFAs might have a beneficial effect on the expression of damage to the CNS by correcting any alterations in eicosanoid production, which is known to be part of the cascade of events following radiation exposure [13]. Of particular interest was the n-6 PUFA, γ-linolenic acid (GLA), and the n-3 PUFA, eicosapentaenoic acid (EPA). GLA will increase the production of monoenoic prostanoids, and EPA will increase the production of trienoic prostanoids, both at the expense of the dienoic pathways that are known to develop a detrimental imbalance after irradiation. The prostaglandins E_1 and I_3 have a number of desirable vascular physiological properties, whereas the thromboxanes A_1 and A_3 have none of the undesirable properties associated with high A_2 levels (e.g., enhanced platelet aggregation leading to increased tendency for intravascular thrombosis and vasocontriction).

In studies in the pig [25], an oil (So-5407) containing both GLA and EPA was used. Oil was administered orally (12 ml/day), starting the day after irradiation with a single dose of 22 Gy and continuing for a period of 20 weeks. Only 1 of 5 pigs that received So-5409 developed paralysis compared with 4 of 5 pigs in a group that received a placebo oil. This difference was highly significant ($P < 0.001$). The results obtained for the placebo group were comparable to those from in a series of animals that received no oils, in which a steep dose-response relationship for spinal cord injury was found (Fig. 5). More recently, El-Agamawi et al [26] showed that an oil containing only GLA significantly delayed the onset of paralysis following irradiation of the spinal cord in young (5-week-old) rats. Thus dietary PUFAs given prophylactically appear to reduce the severity of radiation-induced injury to the CNS significantly. An advantage of the potential clinical use of PUFAs is that they appear to be nontoxic, even when they are administered over long periods [27].

TOLERANCE OF THE CNS–RADIOBIOLOGICAL CONSIDERATIONS

There is now a considerable body of clinical and experimental evidence to suggest that, with conventional radiotherapy involving up to 5 fractions/week, the radiation tolerance of the CNS is highly dependent on the dose per fraction and, hence, on the number of treatments given. The effect of variations in the overall treatment time has been found to be negligible, at least for treatment periods up to 8 weeks.

Extensive sets of data, particularly for the spinal cords of rats, have been used to establish tolerance formulas for possible clinical application when changing dose-fractionation schedules in patients. Two basic approaches have been used. The model currently in more general use is one that links the response to fractionated irradiation to the fractional reproductive survival of clonogenic target cells, i.e.,

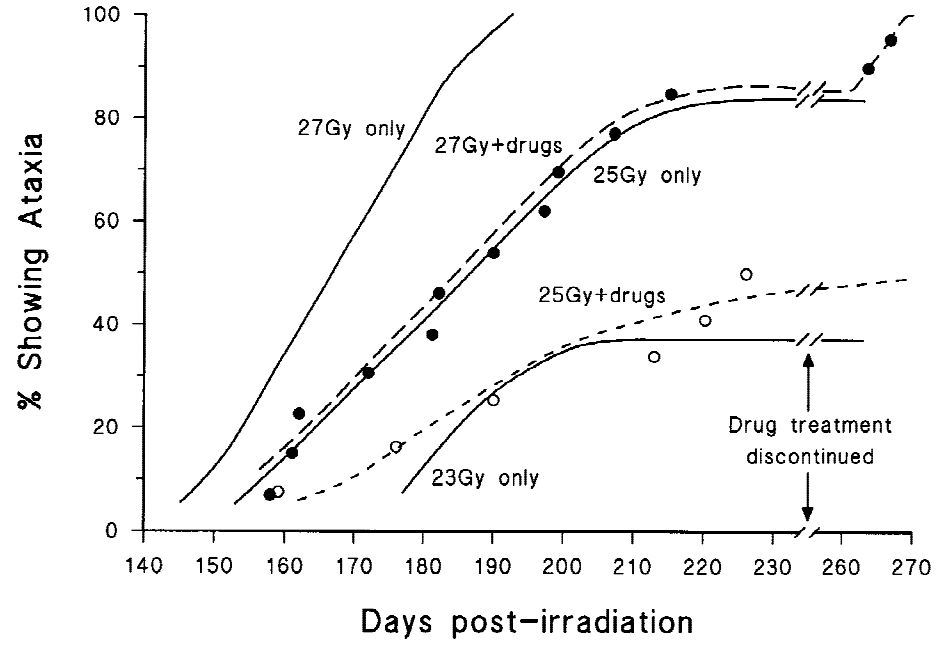

Fig. 4. Dose-related latency for the development of ataxia in rats following irradiation of the cervical spinal cord with 23 Gy, 25 Gy, and 27 Gy alone or with the postirradiation administration of desferrioxamine. Reproduced from Hornsey et al. [22].

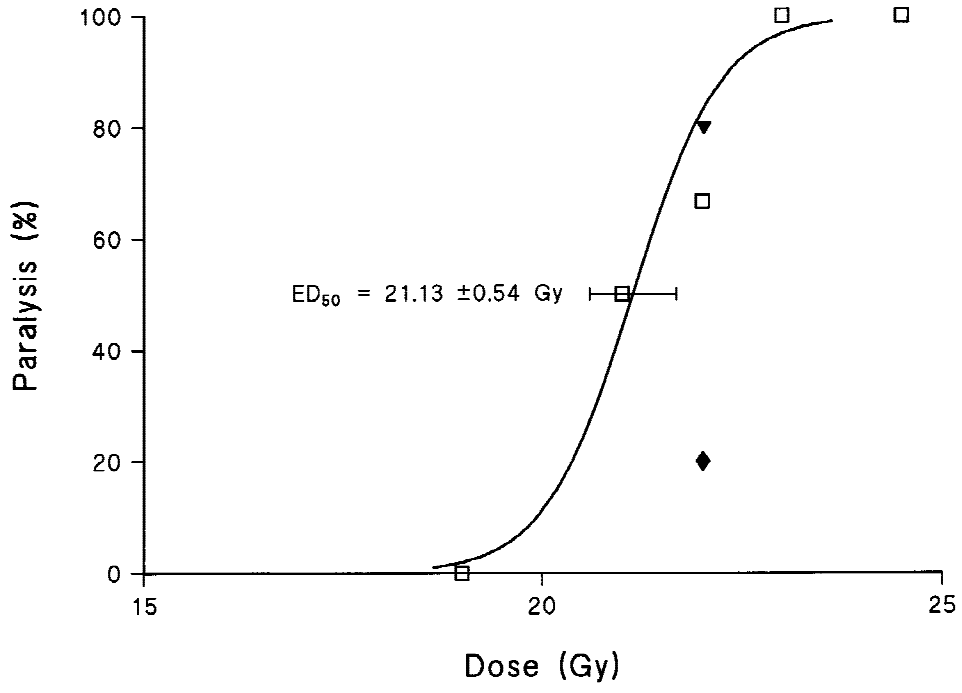

Fig. 5. Dose-related incidence in radiation-induced paralysis in pigs after local irradiation of the cervical spinal cord. Irradiation was given alone (squares) or after 22 Gy was followed by the daily administration of the oil So-5409 (diamond) or a placebo oil (triangle). Reproduced from Hopewell et al. [25].

$$\text{Survival fractions (D)} = e^{-(\alpha D+\beta D^2)}$$

where the surviving fraction (''SD'') for dose ''D'' is determined by two constants, ''α'' and ''β,'' that are related to linear and quadratic determinants of dose ''D,'' respectively. The α/β ratio, with the dimension of dose, is the dose at which the linear and quadratic terms contribute equally to cell inactivation [28].

The above equation can be rewritten as

$$\text{Integral SD} = -nd(\alpha + \beta d) \quad (1)$$

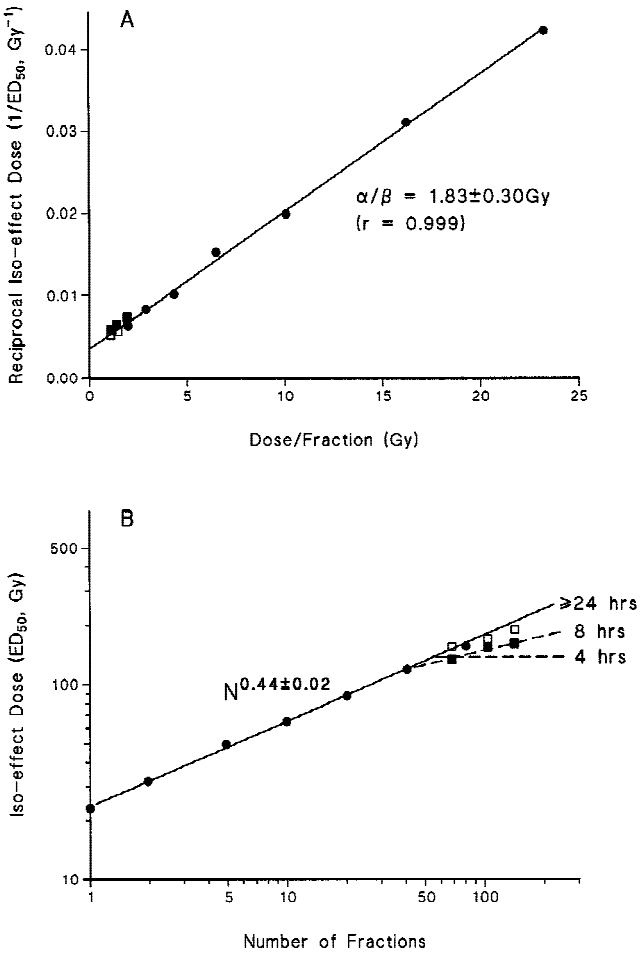

Fig. 6. The response of the cervical spinal cord of rats to fractionated irradiation. **A:** Isoeffective (ED_{50}) dose against dose/fraction. **B:** Isoeffective (ED_{50}) dose for radiation-induced paralysis against fraction number. Dose fractions were given daily (solid line connecting circles in A and B) as two daily fractions separated by 8 hours (dashed line connecting solid squares in B) or by 4 hours (dashed line in B). Open squares indicate correction for incomplete in 8 hours (see text). Based on Ang (personal communication).

for ''n'' fractions of size ''d.'' Then, by replacing ''Integral SD'' with ''E'' and by dividing by ''nd,'' a linear equation can be derived that correlates the reciprocal of the total dose (1/nd) with the dose per fraction (d), such that

$$1/(nd) = \alpha/E + (\beta/E)d \qquad (2)$$

The ratio of the intercept to the slope of the regression line in the equation is the α/β ratio. A more empirical approach to the problem of dose fractionation and CNS tolerance is the basic power-law equation, in which a fraction number exponent, ''N,'' is derived from the slope of a logarithmic plot of isoeffective dose (tolerance) against fraction number.

Most of the valuable clinical and experimental data used to derive parameters for use with both of the above approaches were reviewed recently [2]. This review suggested that, for brain and upper spinal cord, an average α/β ratio of 2 Gy could be used. For doses per fraction of between 2 Gy and 8 Gy, a power-law formulation with an N exponent of 0.4–0.45 seems to be safe.

TABLE I. What Is a Safe Tolerance Dose for the Central Nervous System?

Dose	Reference
Brain	
52 Gy/5 weeks at 2 Gy/fraction	Sheline et al. [30]
50 Gy/25F/35 days or	
54 Gy/30F/42 days	Marks et al. [34]
Spinal cord	
50 Gy/2 Gy fractions	Wara et al. [39]
50 Gy/25F/35 days	Abbatucci et al. [36]
ED_5 57–61 Gy	
ED_{50} 68–73 Gy	Schultheiss et al. [37]
ED_{50} 65 Gy (58–79 Gy)	Reinhold et al. [38]

ED_{50} and ED_5: the radiation doses quoted to produce a 50% or 5% incidence of radiation-myelopathy in patients recovery radiation therapy.

Recent data from Ang et al. (personal communication) are consistent with these findings. An α/β ratio of 1.83 ± 0.3 Gy was obtained. Even results for doses of <2 Gy/fraction, which were given as 2 fractions/day separated by 8 hours, appeared to be consistent with this generalisation (Fig. 6A). When the same data were replotted on a log-log plot, results for daily fractions with ⩾24 hours between doses were consistent with an N exponent of 0.44 ± 0.02. However, results for studies with 2 fractions/day with 8 hours between doses deviated from this prediction and were corrected only partly by an assumption that 10% of any repairable damage was incomplete in 8 hours (Fig. 6B). Early data from the same author [29], suggesting no additional increase in isoeffective dose with dose/fraction of <2 Gy, are included for comparison. In this instance, the interval between 2 fractions/day was only 4 hours, an effect that is likely to be accounted for by the incomplete repair of sublethal damage. For conventional radiotherapy, Sheline et al. [30] also reported a regression line with a slope of 0.44. This was based on data from 40 patients with brain necrosis.

The pattern of the kinetics of repair of sublethal radiation damage remains controversial. Hopewell and van den Aardweg [31] were perhaps the first to suggest that repair may be more complex than the single exponential that was assumed in early mathematical model systems [32]. The most recent evidence for the spinal cord [33] is that the kinetics of repair of sublethal damage are better fitted by a biexponential equation compared with a monoexponential equation, with half-times for repair of 0.7 hours and 4.0 hours, respectively.

The various estimates of safe tolerance doses for the brain and spinal cord of adults are listed in Table I. A total dose of 50 Gy, given as 2 Gy fractions daily over 5

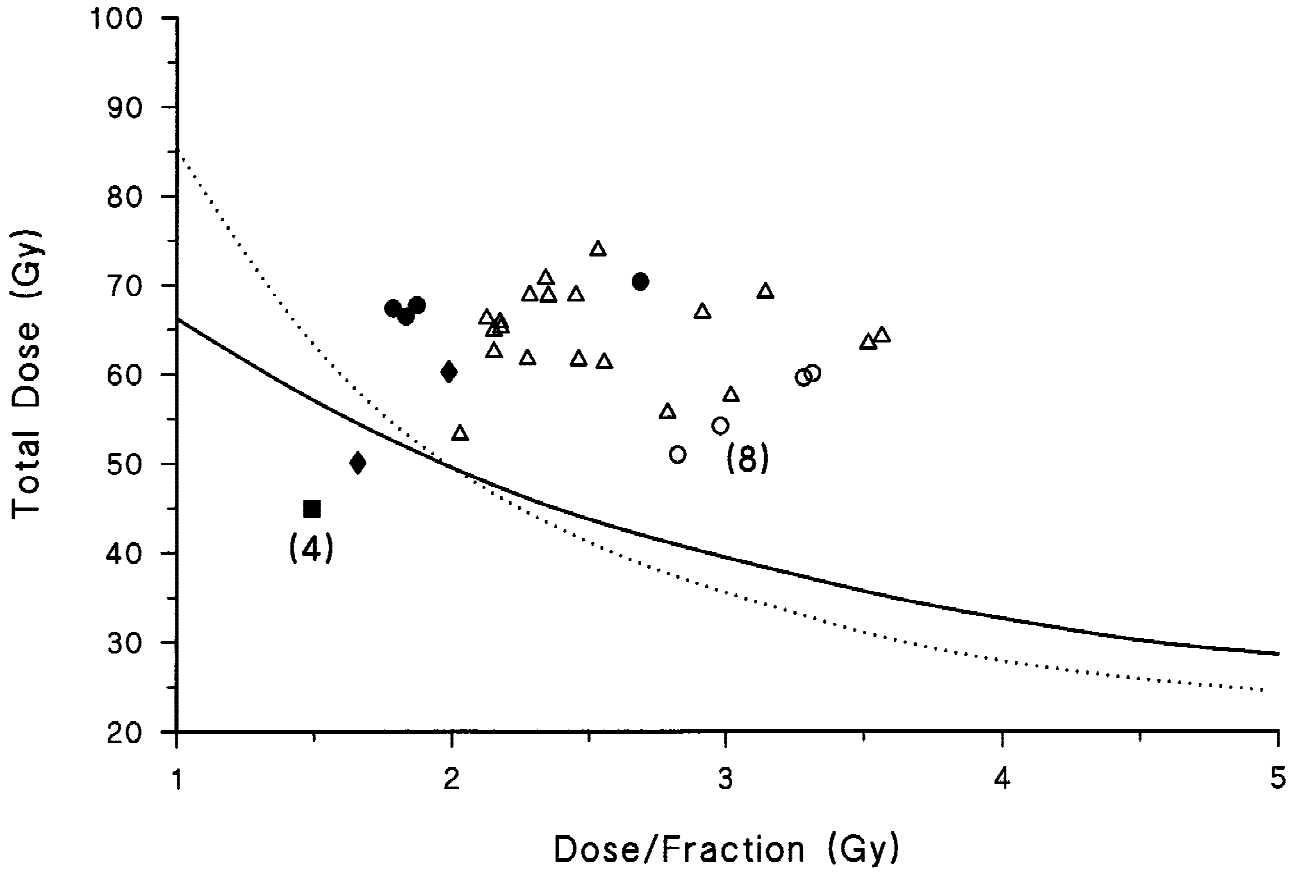

Fig. 7. Relationship between total tolerance dose and dose/fraction for radiation-induced myelopathy in man normalised to 50 gy in 2-Gy fractions. Relationship based on the LQ (α/β ratio 2 Gy) and power-law ($N^{0.44}$) models. Based on van der Kogel [2]. Myelopathy cases as reported by Reinhold et al. [38] (triangles), Wara et al. [35] (solid circles), Abbatucci et al. [36] (open circles), Dische and Saunders [39] (squares), and McCunniff and Liang [40] (diamonds).

weeks, would appear to be a generally accepted standard. Predictions of the variation in total dose with dose per fraction based on this standard are made in Figure 7. Both the linear-quadratic approach and the power-law approach are used. For doses of >2 Gy/fraction, a similar relationship is indicated with the power-law approach, suggesting slightly lower tolerance doses. The reverse is true for doses <2 Gy/fraction. The dosimetric characteristics of many of the reported cases of radiation myelopathy are also indicated on the plot. Most exceed the predictions made by both models. The cases of myelopathy below the line involved treatment with multiple fractions per day. An inappropriate allowance for incomplete repair, with short ($\leqslant$6 hours) interfraction intervals, would appear to provide an adequate explanation for these cases.

EFFECTS OF AGE AND RADIOBIOLOGICAL FACTORS ON THE RADIATION TOLERANCE OF THE CNS

The question of whether the immature CNS is more at risk of developing radiation-induced toxicity, specifically, for the end point of white matter necrosis, has been investigated in animal studies. However, the generalised atrophy of nerve tissue at doses that are not associated with a significant risk of early delayed white matter necrosis or late delayed gross vascular abnormalities may be evaluated from clinical studies, because, in children, these may have an effect on intellectual ability.

The effects of age have been studied extensively by using the rat spinal cord model [41]. Rats between 2 weeks of age and maturity showed no marked variation in radiosensitivity, as assessed by the dose-related incidence of myelopathy. Only very immature rats (1 week old) were found to be more radiosensitive. The ED_{50} for myelopathy was reduced by ~10% compared with older animals. The most marked effect of age was in the latency to paresis. This was reduced progressively from approximately 200 days in young adult rats to 30 days in animals that were irradiated with 22 Gy at 2 weeks of age.

There is no simple way to determine how findings of this type might be extrapolated to children and adolescents, particularly in terms of the effects of treatment on

intellectual development. Some reports of neurological complications in children must be interpreted with caution, because chemotherapy and, in particular, intrathecal methotrexate were administered. This is particularly true for patients with acute lymphoblastic leukaemia (ALL), who could receive cranial irradiation with or without methotrexate or even methotrexate alone prior to total body irradiation (TBI). TBI was used as conditioning for bone marrow transplantation (BMT) [42]. Although no age-dependent, maximum tolerated dose has been determined, early papers by Bloom et al. [43] proposed that children 3–5 years of age and those under 3 years of age should not receive doses in excess of 20% and 33% less than the total adult dose, respectively. For a 20% reduction in total dose, this would translate to the equivalent of 40 Gy in 25 fractions for children compared with the standard 50 Gy in 25 fractions for adults. The biological effect of any revised schedule, as pointed out previously, can be deduced only by making reference to one of the tolerance formulas. A simple equation proposed by Thames and Hendry [44] was that the total effect (TE) of any treatment could be compared by using

$$TE = (\alpha/\beta + d)\, Nd$$

where ''d'' is the dose per fraction, ''N'' is the fraction number, and α/β is 2 Gy for CNS tissue. Thus, the 20% reduction in total dose proposed by Bloom et al. [43] for children 3–5 years of age represents a 28% reduction in biologically effective dose (TE $= 144$ units compared with the standard treatment of 200 units).

In results from a recent analysis of children who received cranial irradiation for ALL followed by TBI prior to BMT [42], 15 of 21 patients received biologically effective doses in excess of 144 units. However, in all of the cases, there was a considerable interval between the initial local cranial irradiation and TBI. TBI treatment was equivalent to approximately 50% of the full adult CNS tolerance dose, and, in all of the cases, this was always given to children >5 years of age. The worst outcomes were in those children who were young at the time of initial cranial irradiation (<4 years of age), who later suffered CNS relapse and, inclusive of the TBI, who received the highest total dose of cranial irradiation. The most severely affected children were approximately 3 years of age at the time of the initial cranial irradiation and had received biologically effective doses close to the maximum tolerated adult dose. This is an area in which continued caution is needed, but it can be concluded that cranial irradiation associated with TBI does not necessarily lead to a poor functional outcome if radiobiology parameters are taken into account.

CONCLUSIONS

In conclusion, the biological basis of late radiation-induced damage to the CNS is now understood more fully, and the first attempts to modulate its expression have been carried out successfully in animal models. Knowledge of the radiobiological factors that influence normal CNS tolerance now enable us to calculate, with some degree of certainty, the biological effectiveness of radiation treatment. This is important in paediatric cases in which schedules have to be modified frequently. These different factors suggest that there are now real prospects for an improvement in the therapeutic ratio for radiotherapy in the treatment of childhood malignancies involving the CNS.

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